The ALSFRSr predicts survival time in an ALS clinic population

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Abstract—*Objective:* To determine whether the Amyotrophic Lateral Sclerosis Functional Rating Scale–revised (ALSFRSr), a predictor of survival time in ALS clinical trials, predicts survival time in an ALS clinic population. *Methods:* The authors prospectively evaluated 267 consecutive patients with ALS at first visit to an ALS clinic using the ALSFRSr and pulmonary function testing. The association of ALSFRSr score at baseline with death or tracheostomy in ALS was examined using Cox proportional hazards models, adjusting for age at baseline, sex, and symptom duration. *Results:* Of 267 patients with ALS, 103 (39%) reached the endpoint, defined as either death (79 patients) or tracheostomy (24 patients), during a mean follow-up of 1.0 ± 0.7 years. Among the 103 patients who reached the endpoint during follow-up, 77 (75%) had a baseline ALSFRSr score of less than 38 (the median baseline score of all patients), compared to 53 of 164 (32%) who remained alive without tracheostomy. Patients with a total ALSFRSr score below the median had a 4.4-fold increased risk of death or tracheostomy compared to those who scored above the median (HR: 4.38, 95% CI: 2.79 to 6.86, $p < 0.001$). Both the total ALSFRSr score at baseline (HR: 0.94, 95% CI: 0.91 to 0.98, $p < 0.001$) and forced vital capacity at baseline (HR: 0.99, 95% CI: 0.98 to 1.00, $p = 0.02$) were associated with death or tracheostomy when included in the same Cox model. *Conclusions:* In an ALS clinic population, the total Amyotrophic Lateral Sclerosis Functional Rating Scale–revised score at baseline is a strong predictor of death or tracheostomy independently of forced vital capacity and after adjustment for age at baseline, sex, and symptom duration.

NEUROLOGY 2005;64:38–43

Clinical trials in ALS have used the following primary outcomes: mortality,[1-4] pulmonary function,[2] muscle strength,[5-8] and neurologic impairment and disability.[9,10] The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) or its revised version (ALSFRSr), a disease-specific functional rating scale, was a secondary outcome measure in several trials.[2,3,5,7,8,11] Favorable properties of the scale include the following: 1) It is patient-centered, measuring function from the patient's perspective. 2) It is cost-efficient and, unlike muscle strength testing, does not require special equipment. 3) Administration by telephone shows good correlation with in-clinic administration and can be used when patients can no longer travel to the clinic.[12] 4) Internal consistency and test-retest reliability are excellent.[13,14] 5) Construct validity is evident because it correlates well with a non-disease specific, validated functional rating scale, the Sickness Impact Profile (SIP),[13-15] with the Schwab and England Scale, a widely used instrument to score activities of daily living,[15] and with measures of muscle strength.[13] 6) Most importantly, it has been validated as predictor of survival time based on data from ALS trials.[2,14,16,17]

The generalizability of the finding that the ALSFRSr is a predictor of survival time is unclear for several reasons. First, the follow-up time in some of the clinical trials was limited to the relatively short period of 6 to 9 months.[2,7,9,11,14,16] Second, patients who did not meet all El Escorial criteria for probable or definite ALS were excluded.[2,3,5,7,8,14,16,17] Third, studies using quantitative muscle strength testing as primary outcome measure excluded both patients with bulbar and respiratory ALS and patients who were unable to perform quantitative strength testing due to advanced muscle weakness.[7,8,11,16,17] Finally, many trials excluded patients below a minimum forced vital capacity (FVC) or a limiting score on a functional rating scale.[2,3,5,7,8,16,17] These restrictive criteria might make clinical trial sample data inapplicable to the general ALS population. A prior study using an ALS clinical database to identify predictors of survival was limited by missing data points, excluding 92 of 247 patients from the analysis, and did not provide an estimate of the strength of the association between ALSFRSr and mortality.[16]

Validating the ALSFRSr as a predictor of survival time outside the clinical trial experience has two benefits. 1) It may encourage clinicians to accept that the results of trials using it as a primary outcome measure are applicable to the general ALS population. 2) In the clinical setting, it may provide an

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Supported by an Irving Scholar Award (P.K.), K12 Award (P.K.), Muscular Dystrophy Association "Wings over Wall Street" (H.M.), NINDS R01 NS 48125 (P.K.), NINDS R01 NS48555 (G.L., J.L.P.T., B.L.).

Received February 10, 2004. Accepted in final form September 15, 2004.

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easily administered instrument for better prognostication and management of ALS patients.

To study the validity of the total baseline ALSFRSr score and subscores as a predictor of survival time beyond the constraints of a clinical trial, we analyzed longitudinal data from an ALS clinic population.

Methods. *Patients and procedures.* In December 1999, we began administering the ALSFRSr to all patients who were cared for at the Eleanor and Lou Gehrig MDA/ALS Research Center in New York City, a tertiary care center. We prospectively collected data and included consecutive patients who came to the center for an initial visit between December 1999 and July 2003 with the diagnosis of suspected, possible, probable, or definite ALS according to the initial El Escorial Criteria.[19] The number of patients cared for at the center has increased in recent years so that more patients were seen during the second half of the study period. Patients who came to the center during their diagnostic workup but subsequently received their ongoing care elsewhere were excluded. The protocol for this study was approved by the Columbia University Medical Center Institutional Review Board.

Between 1 and 6 months following their initial diagnostic consultation, patients were referred by one of the ALS center's physicians to receive their ongoing ALS care at the multidisciplinary ALS clinic. At the baseline visit to this clinic, we documented demographic and clinical information, including age, sex, and date and site of symptom onset. Symptom duration was defined as the time period between reported onset and baseline evaluation. Site of symptom onset was categorized into four groups (upper extremity, lower extremity, bulbar, or respiratory onset) according to the patient's report. In addition to the medical history and neurologic examination, the baseline evaluation included the ALSFRSr and FVC. The original ALSFRS is a questionnaire-based, 10-item functional scale administered by an evaluator to the patient or, if the patient cannot communicate effectively, to an informant (spouse or other caregiver).[18] The revised scale (ALSFRSr) incorporates three items assessing respiratory function, replacing one item in the original ALSFRS. The ALSFRSr contains 12 items rated from 0 (complete dependence for that function) to 4 (normal function), resulting in a total ALSFRSr score ranging from 0 to 48. The items fall into four clinical domain subscores, each containing three items: 1) bulbar function, 2) fine motor function, 3) gross motor function, and 4) respiratory function.[14]

During the follow-up period, we collected information on date of death and tracheostomy for institution of permanent mechanical ventilation. Although we intended to see patients every 3 months, intervals between visits varied. In the terminal stages of the disease, many patients could not come to the center, but care was delivered remotely through telephone contact, e-mail, home visits, and in collaboration with home health care and hospice agencies.

All patients with 1) ALSFRSr score at baseline visit and 2) known survival status were included in the analysis. Of 274 consecutive patients who had ALSFRSr at baseline, 7 (2.6%) were excluded because we had no survival status information, leaving 267 patients for analysis. No significant differences were observed between excluded ($n = 7$) and included patients ($n = 267$) for age, sex, symptom duration, site of symptom onset, total ALSFRSr score, or FVC. Seventeen of 267 patients (6.4%) were lacking information for FVC because spirometry was not performed if there were technical problems in patients with poor lip seal or impaired cognition or if there were time constraints in the busy multidisciplinary care setting.

Data analysis. We compared baseline demographic and clinical characteristics of ALS patients who died or had tracheostomy during follow-up and those who did not, using Student's t-test for continuous variables and a χ^2 test for categorical variables. When the assumption of normal distribution for a given baseline variable was not reasonable based on visual inspection of the histograms, we used the Wilcoxon's rank sum test instead of the t-test. Time to endpoint was the time from baseline to death or tracheostomy; patients who remained alive without tracheostomy were censored at study end (July 24, 2003). The association of the total ALSFRSr score and subscores at baseline with death or tracheostomy was analyzed using Cox proportional hazards models, adjusting for age at baseline, sex, and symptom duration.[20] We also investigated this association by including the total ALSFRSr score together with potential confounding clinical variables, such as FVC (% predicted), riluzole use (ever vs never), and site of symptom onset, in separate Cox models. Finally, we included the total ALSFRSr score and the other significant or clinically meaningful covariates in the same Cox model. Categorical variables were inserted into the Cox models as dummy variables. The Kaplan-Meier method was used to plot survival curves.[21]

Two sets of supplementary analyses were conducted. First, we fit two Cox models using 1) the ALSFRSr score at each visit and 2) the ALSFRSr score change from baseline at each visit (total ALSFRSr score at baseline − total ALSFRSr score at each visit) as time-dependent covariates in separate models. Because the interval and frequency of follow-up visits varied and many patients with advanced disease could not come to the center, we had to impute the ALSFRSr score for 2,586 of 3,204 (81%) "monthly visits," as required by our choice of monthly intervals for the time-dependent covariate analysis. The imputation procedure used linear interpolation between two known ALSFRSr scores. (For patients with only the baseline visit, a slope was calculated by using symptom duration and the ALSFRSr score at baseline, and assuming a maximum score of 48 at symptom onset.)

Second, given the heterogeneity of the clinical manifestations of ALS, i.e., differences in the site of symptom onset and different patterns of spread to other body regions, we postulated that defining a most affected domain subscore of the ALSFRSr for each patient might provide a sensitive alternative outcome measure for ALS trials. As a first step in assessing the most affected domain subscore as a possible outcome measure, we investigated the association of the most affected subscore of the ALSFRSr with death or tracheostomy. The most affected ALSFRSr subscore was defined as the lowest value at baseline evaluation among the fine motor, gross motor, bulbar, and respiratory clinical domain subscores for each patient. The most affected subscore was the gross motor subscore for 103 (38.6%) patients, fine motor for 70 (26.2%), bulbar for 50 (18.7%), and respiratory for 6 (2.2%). In 38 (14.2%) patients two domain subscores had equally low values.

All statistical analyses were predetermined with the exception of the Cox models with time-dependent covariates and an analysis stratifying the sample into two subsets of patients with total ALSFRSr score above and below the median and including the total ALSFRSr score in the models as a continuous variable.

Results. *Demographic and clinical characteristics of ALS patients.* A total of 103 (38.6%) of 267 patients died ($n = 79$) or had tracheostomy ($n = 24$). The mean duration of follow-up for the whole sample ($n = 267$) was 1.0 year (SD 0.7, median 0.9, minimum 0.01, maximum 2.6). The mean time to death or tracheostomy ($n = 103$) was 0.8 years (SD 0.6, median 0.7, minimum 0.01, maximum 2.3). Compared to the patients who were still alive without tracheostomy, those who died or went on permanent ventilation had significantly shorter symptom duration, lower baseline total ALSFRSr score, and FVC. Patients who died or had tracheostomy also had respiratory onset significantly more often and upper extremity onset significantly less often than patients who did not (table 1).

Patients who died or had tracheostomy used noninvasive positive pressure ventilation (57.3% vs 22.0%, $p < 0.001$) or percutaneous endoscopic gastrostomy (PEG) (42.7% vs 11.0%, $p < 0.001$) more often than patients who remained alive without permanent ventilation. Ninety of 267 patients (33.7%) used riluzole during follow-up with no significant difference between the two groups (31.1% of those who died or had tracheostomy vs 35.4% of those who did not, $p = 0.5$).

Association of the baseline ALSFRSr with mortality. Patients with a baseline total ALSFRSr score below the median score of 38 had a 4.4-fold increased risk of death or tracheostomy compared to patients with a score above the median (HR: 4.38, 95% CI: 2.79 to 6.86, $p < 0.001$), adjust-

Table 1 Baseline demographic and clinical characteristics of ALS patients who died or had tracheostomy during follow-up compared to those who remained alive without tracheostomy

Variable	Deceased or tracheostomy, n = 103	Alive without tracheostomy, n = 164	Total, n = 267
Age, y	63.3 (13.5)	60.7 (12.5)	61.7 (12.9)
% Male	60.5	57.3	54.7
Age at onset, y	59.9 (13.6)	57.1 (13.1)	58.2 (13.3)
Symptom duration, y*	1.5 (1.6)	2.5 (3.4)	2.2 (2.9)
Site of symptom onset*			
Upper extremity†	20.4	39.0	31.5
Lower extremity	36.8	39.0	39.0
Bulbar	33.0	21.3	26.5
Respiratory†	7.8	0.6	3.4
Forced vital capacity (% predicted)*‡	60.1 (24.7)	79.8 (21.8)	72.1 (24.9)
ALSFRSr scores			
Total (range 0–48)*	31.7 (7.7)	38.7 (7.1)	36.0 (8.1)
Fine motor subscore (range 0–12)*	7.0 (3.6)	8.9 (2.9)	8.1 (3.3)
Gross motor subscore (range 0–12)*	6.1 (3.4)	8.1 (3.2)	7.3 (3.4)
Bulbar subscore (range 0–12)*	8.6 (3.4)	10.3 (2.6)	9.6 (3.0)
Respiratory subscore (range 0–12)*	10.1 (2.4)	11.5 (1.2)	10.9 (1.9)
Most affected subscore (range 0–12)*	4.4 (2.6)	6.8 (2.8)	5.9 (3.0)

Values are mean (SD) or %.

* $p < 0.05$ for the comparison of deceased or tracheostomy vs alive without tracheostomy.
† $p < 0.05$ for the comparison of individual sites of symptom onset adjusting for multiple comparisons.[30]
‡ Total n = 250.

ALSFRSr = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised.

ing for age at baseline, sex, and symptom duration. The mean survival time for patients with baseline total ALSFRSr above the median was 25.2 months (SE 1.0), compared to 14.6 months (SE 1.0, median survival 14.2) for those with baseline total ALSFRSr score below the median. When patients were categorized according to quartiles of the total baseline ALSFRSr score, the risk of death or tracheostomy increased progressively from the highest to the lowest quartile (test for linear trend, $p < 0.001$) (table 2 and figure, A).

Both the total ALSFRSr score (HR: 0.91, 95% CI: 0.89 to 0.93, $p < 0.001$) and the FVC (HR: 0.97, 95% CI: 0.97 to 0.98, $p < 0.001$) were predictors of death or tracheostomy when included as continuous variables in separate Cox models. When both the total ALSFRSr score and the FVC were included in the same model, both remained significant predictors of death/tracheostomy. Similarly, the association of the total ALSFRSr score with death or tracheostomy was not changed by including riluzole use or site of symptom onset in the Cox models (see table 2).

We also investigated the association of the total ALSFRSr score at baseline (as a continuous variable) with death or tracheostomy separately for the subsets of patients with total ALSFRSr score above and below the median (≥38 and <38). The total baseline ALSFRSr score remained a predictor in both subsets of patients (HR: 0.71, 95% CI: 0.59 to 0.84, $p < 0.001$ for patients with ALSFRSr score above the median and HR: 0.95, 95% CI: 0.92 to 0.98, $p = 0.002$ for patients with ALSFRSr score below the median).

When we analyzed the four subscores of the ALSFRSr instead of the total ALSFRSr score, the respiratory and gross motor subscores were independent significant predictors of death/tracheostomy (see table 2). The respiratory subscore showed a correlation with the FVC (Pearson correlation, $r = 0.53$, $p < 0.001$).

In a final model including all relevant demographic and clinical covariates, age at baseline, symptom duration, total ALSFRSr score, and site of symptom onset were independent significant predictors of mortality in this ALS clinic population. For each one-point decrease in the total baseline ALSFRSr score, there was a 7% increase in the risk of death or tracheostomy (HR: 0.93, 95% CI: 0.90 to 0.96, $p < 0.001$) (table 3).

Supplementary analyses. We fit two Cox models with time-dependent covariates, adjusting for age at baseline, sex, and symptom duration at baseline. In the first model, the total ALSFRSr score at each study visit was a predictor of death/tracheostomy (HR: 0.90, 95% CI: 0.89 to 0.92, $p < 0.001$). In the second model, we included the total ALSFRSr score at baseline as a time-fixed covariate and the ALSFRSr score change from baseline at each visit as a time-dependent covariate. In this latter model, the total ALSFRSr score at baseline (HR: 0.91, 95% CI: 0.89 to 0.94, $p < 0.001$) and the ALSFRSr score change at each visit (HR: 1.12, 95% CI: 1.09 to 1.15, $p < 0.001$) were independent predictors of death/tracheostomy.

When we investigated the association of the most affected ALSFRSr subscore with death/tracheostomy, we observed a 4.4-fold increased risk for patients with the most affected subscore below the median compared to those with the most affected subscore above the median. The risk increased progressively from the highest to the lowest quartile (test for linear trend, $p < 0.001$). In a Cox model adjusting for age at baseline, sex, and symptom duration, there was a 24% increase in the risk of death/tracheostomy for each one-point decrease in the most affected subscore (HR: 0.76, 95% CI: 0.70 to 0.81, $p < 0.001$) (see table 2 and figure, B).

Finally, we used a backward stepwise selection procedure (entry criterion: $p < 0.05$, exclusion criterion: $p > 0.1$) to select the best predictors among the four subscores of the ALSFRSr (fine motor, gross motor, bulbar, and respiratory) and the most affected subscore. In this analysis, the respiratory (HR: 0.80, 95% CI: 0.73 to 0.87, $p < 0.001$) and most affected (HR: 0.79, 95% CI: 0.73 to 0.85, $p < 0.001$) subscores were retained in the model.

Discussion. Based on our data, the total ALSFRSr score at initial visit strongly predicted survival time in an ALS clinic population, after adjustment for age at baseline, sex, and symptom duration. We also

Table 2 Association of the baseline ALSFRSr and other clinical characteristics with death or tracheostomy, from Cox proportional hazards models adjusting for age at baseline, sex, and symptom duration (n = 267)

Model	Variable	Hazard ratio (95% CI)	*p* Value
1	Total ALSFRSr score (dichotomized at the median)		
	≥38	1.00 (Reference)	
	<38	4.38 (2.79–6.86)	<0.001
2	Total ALSFRSr score quartiles		
	≥43	1.00 (Reference)	
	≥38 and <43	7.08 (2.12–23.66)	0.001
	≥33 and <38	12.51 (3.81–41.08)	<0.001
	<33	27.78 (8.57–90.07)	<0.001
3	Total ALSFRSr score	0.91 (0.89–0.93)	<0.001
4*	Total ALSFRSr score	0.94 (0.91–0.98)	<0.001
	Forced vital capacity (% predicted)	0.99 (0.98–1.00)	0.02
5	Total ALSFRSr score	0.91 (0.89–0.93)	<0.001
	Riluzole use (ever vs never)	0.92 (0.60–1.41)	0.7
6	Total ALSFRSr score	0.91 (0.89–0.93)	<0.001
	Site of symptom onset		
	Upper extremity	1.00 (Reference)	
	Lower extremity	1.28 (0.73–2.23)	0.4
	Bulbar	1.91 (1.06–3.46)	0.03
	Respiratory	8.44 (3.68–19.35)	<0.001
7	Fine motor ALSFRSr subscore	0.95 (0.88–1.03)	0.2
	Gross motor ALSFRSr subscore	0.91 (0.84–0.99)	0.02
	Bulbar ALSFRSr subscore	0.94 (0.88–1.01)	0.08
	Respiratory ALSFRSr subscore	0.79 (0.72–0.87)	<0.001
8	Most affected ALSFRSr subscore (dichotomized at the median)		
	≥7	1.00 (Reference)	
	<7	4.44 (2.73–7.22)	<0.001
9	Most affected ALSFRSr subscore quartiles		
	≥9	1.00 (Reference)	
	≥7 and <9	4.46 (1.32–15.22)	0.02
	≥4 and <7	10.33 (3.18–33.57)	<0.001
	<4	20.60 (6.31–67.30)	<0.001
10	Most affected ALSFRSr subscore	0.76 (0.70–0.81)	<0.001

* n = 250.

ALSFRSr = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised.

found an independent effect of the baseline total ALSFRSr score on death/tracheostomy in Cox models including FVC and riluzole use. These findings are consistent with the ALS clinical trial results.[2,7,8,14,16,17] The robust association between ALSFRSr and death/tracheostomy was remarkable given that the clinic setting is less controlled than the clinical trial environment and does not provide consistent raters or continuous training and evaluation of raters. Also, our experience indicates that the ALSFRSr can be successfully administered in a busy multidisciplinary clinic. Larger studies are needed to obtain narrower CIs for relative risk estimates and thus allow better assessment of the sensitivity of the ALSFRSr to predict small changes in mortality.

Among the ALSFRSr subscores, the respiratory score was the strongest predictor of survival time, as expected because death in ALS is ultimately due to

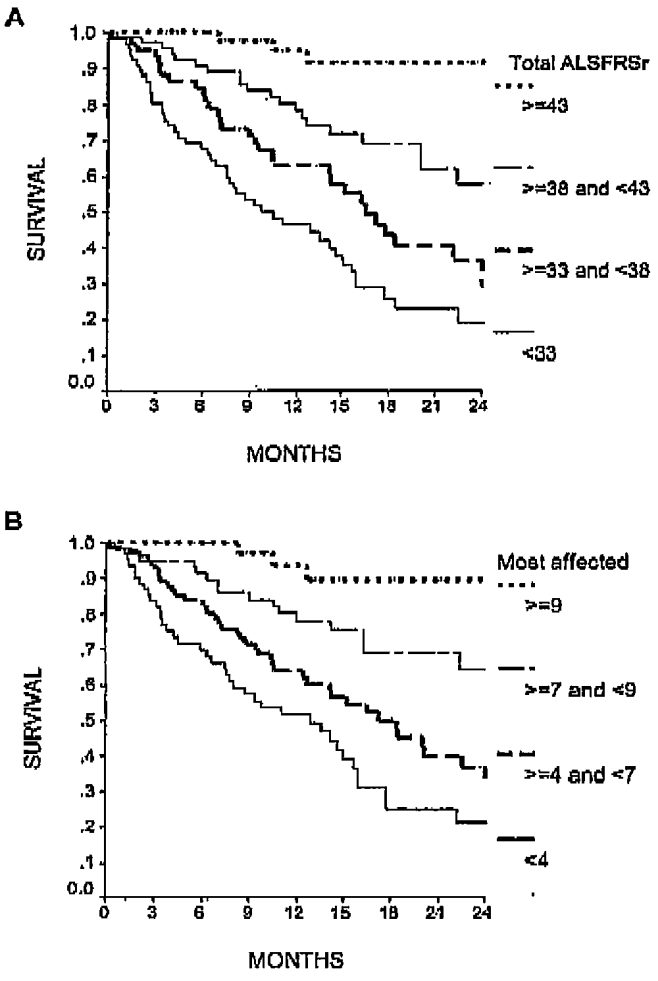

Figure. Kaplan-Meier survival plots (endpoint: death or tracheostomy) in an amyotrophic lateral sclerosis clinic population (n = 267), according to quartiles of the total Amyotrophic Lateral Sclerosis Functional Rating Scale–revised (ALSFRSr) score (A) and the most affected subscore of the ALSFRSr (B).

respiratory failure. While respiratory subscore and FVC were correlated, the respiratory subscore did not account for much of the FVC variation ($r = 0.53$, $r^2 = 0.28$). The correlation in our study was higher than in the BDNF clinical trial ($r = 0.33$),[14] which may in part be attributed to the wider range of disease severity in our patients. The FVC was a significant predictor of mortality in several clinical trials,[16,17] but not in this study when other clinically meaningful covariates were included in the model. Symptom duration at baseline visit was a significant predictor of survival time (shorter duration was associated with higher mortality) in our study, as in others.[22-24] A possible interpretation is that symptom duration at first visit may be a measure of the rate of disease progression, because patients who have more rapidly progressive symptoms go to physicians sooner.

***Table 3** Predictors of death or tracheostomy in an ALS clinic population (n = 260)**

Variable	Hazard ratio (95% CI)	p Value
Age at baseline, y	1.02 (1.01–1.04)	0.01
Male vs female	0.85 (0.53–1.35)	0.5
Symptom duration, y	0.74 (0.63–0.87)	<0.001
Total ALSFRSr score	0.93 (0.90–0.96)	<0.001
Forced vital capacity, % predicted	0.99 (0.98–1.01)	0.3
Riluzole use, ever vs never	0.85 (0.54–1.33)	0.5
Site of symptom onset		
Upper extremity	1.00 (Reference)	
Lower extremity	1.17 (0.66–2.07)	0.6
Bulbar	1.81 (0.99–3.33)	0.05
Respiratory	6.52 (2.72–15.60)	<0.001

* All variables were included in the same Cox proportional hazards model.

ALSFRSr = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised.

The strong association of the most affected subscore of the ALSFRSr with mortality suggests that a measure that considers the clinical heterogeneity of ALS provides an alternative outcome measure, which may prove to be more sensitive than the total ALSFRSr score for ALS clinical trials.

The main strength of our study is that, compared to patients in clinical trials who must meet restrictive inclusion criteria, our patient sample is probably more representative of the general ALS population. Our patients, who attend a tertiary ALS center, may be self-selected by access to information and medical care, although some of them attended a clinic for the poor. Also, our study population is not an incidence cohort and thus further research on incidence cases is needed to determine the validity of the ALSFRSr as a predictor of mortality in the general ALS population.

Our study has limitations. Our sample presented a relatively long mean symptom duration (2.2, SD 2.9 years) and low mean ALSFRSr score (36.0, SD 8.1) at baseline, which might indicate that our findings are not applicable to a less severe clinic sample of ALS patients. However, the effect of the ALSFRSr was even stronger when we analyzed separately the subsample of patients with ALSFRSr score above the median. Noninvasive, positive pressure ventilation[25] and PEG[26] are associated with increased mortality in ALS trials and a clinical database,[27] implying that these therapies are markers of advanced disease. A population-based study[28] has confirmed the increased survival in patients taking riluzole, reported in clinical trials.[1,4] However, our data did not allow detailed analyses of these therapeutic interventions, because accurate data on timing or compliance with these interventions were not recorded in sufficient detail. It has also been suggested that the decline in

ALSFRS scores for a group of patients is a stronger predictor of mortality than the initial score.[16,17] Although our primary analysis used the initial ALSFRSr score, we have conducted secondary analyses with ALSFRSr as a time-dependent covariate and found that the ALSFRSr at each visit as well as the change in ALSFRSr score from baseline (independently of the baseline ALSFRSr score) are significant predictors of survival time in ALS. These analyses suggest that changes over time in the ALSFRSr score reflect disease progression, and thus further support its role as a predictor of survival time in ALS. However, the results of these secondary time-dependent analyses have limitations since data for most of the visits had to be imputed, because the interval and frequency of follow-up visits varied in our sample. Many patients with advanced disease could not come to the center, and telephone administration of the ALSFRSr has not been part of our clinical practice.

Whereas further research is needed to determine whether the ALSFRSr has sufficient sensitivity to detect small changes in mortality, the potential advantages of the ALSFRSr for clinical trials are shorter follow-up period (compared to mortality as outcome measure) and wider participation of patients and clinicians outside University-based ALS centers (compared to outcome measures requiring special equipment such as quantitative muscle strength testing). These are important considerations for ALS clinical trials given the limited pool of patients and the number of new treatments awaiting testing.[29]

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